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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOLLENBERGER, LOUIS V	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/562,677	LI ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9 and 11-21* is/are pending in the application.

4a) Of the above claim(s) *4,7,9,15 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,6,8,11-14,16-18,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 3/16/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 9/15/2008 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's amendment to the claims, filed 3/16/2009, is acknowledged. With entry of the amendment, claims 1, 3-9, and 11-21 are pending.

Claims 4, 7, 9, 15, and 19 remain withdrawn pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim.

Claims 1, 3, 5, 6, 8, 11-14, 16-18, 20, and 21 are under consideration.

Election/Restrictions

The previous Action acknowledged Applicant's election without traverse of (1) "an increase in the amplitude of the signal," (2) "an addition of a functional group," (3) a phosphatase, (4) AMP being the substrate, and (5) "increase in signal intensity."

During a telephone conversation with Attorney for Applicant, Jenny Chen, on 9/9/08 a provisional election was made to prosecute the invention of claim 8 (removal of a functional group), not claim 7 (addition of a functional group) as originally elected in the response. The corrected election is in keeping with the elections of a phosphatase and AMP.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The U.S. Court of Appeals Federal Circuit decision in *Pfizer Inc. v. Teva Pharmaceuticals USA Inc.*, 86 USPQ2d 1001 (Fed. Cir. 2008) makes it clear that the protection afforded by 35 USC 121 applies only to divisional applications filed as the result of a restriction requirement.

Claims 1, 3, 5, 6, 8, 11-14, 16-18, 20, and 21 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6, and 24-35 of copending Application No. 10/502,190.

The conflicting application claims a signaling aptamer complex for the detection of a target, comprising 1) an aptamer having a AMP target binding domain and a complementary oligonucleotide binding domain, 2) a complementary oligonucleotide bound to said

complementary oligonucleotide binding domain, 3) a fluorophore, and 4) a quencher, wherein upon binding of AMP to said aptamer said complementary oligonucleotide is released and a fluorescent signal is generated.

The instant application is drawn to a method of using "a signaling aptamer" to monitor the enzymatic conversion of a first substance A to a second substance B. Obvious variations of the method, including detecting the presence of the enzyme or inhibitors of said enzyme, are also claimed. In certain embodiments substance A is AMP and the enzyme is phosphatase. The instant claims further define the signaling aptamer as "a signaling aptamer complex," having features identical to those of the signaling aptamer complex claimed in the '190 application.

One of skill would instantly recognize the signaling aptamer complex claimed in the conflicting '190 application for the detection of AMP, could be used to detect and quantify the presence of AMP in essentially any suitable aqueous solution (i.e., test sample) regardless of how the AMP was produced, whether chemical or enzymatic. In view of the level of skill and knowledge in the art of fluorescent-based biochemical assays, it would further have been obvious the claimed signaling aptamer complex could be used to monitor the ongoing production of AMP in a solution by simply monitoring the change (e.g., increase) in fluorescence over time, using standard fluorescence detection equipment and techniques.

Therefore, one of ordinary skill in the art would conclude that the methods defined in the claims at issue for monitoring the enzymatic production of AMP or any other enzymatic product would have been obvious use of the signaling aptamer complex defined by the claims in conflicting application 10/502,190.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant traverses the ODP rejection on the grounds the conflicting claims are drawn to related but patentably distinct inventions, inasmuch as the conflicting application is drawn to a product, and the instant application to a process of using that product. In support thereof, Applicant cites MPEP 806.05(h) and form paragraph 8.20, and, in the manner commonly used by Examiners to show reason for restriction between products and processes of use, sets forth examples of materially different products that may be used to practice the process and materially different processes in which the product may be used.

Applicant's arguments have been fully considered. However, Chapter 800 of the MPEP, and more specifically section 806.05(h), is limited to the subject of restriction and double patenting as it relates to national applications filed under 35 U.S.C. 111(a). The instant application was filed under 35 USC 371. Restriction between two or more inventions in a national stage application filed under 35 USC 371 is governed by articles and rules of Unity of Invention discussed in Chapter 1800, section 1850, of the MPEP. Insofar as the instant application, the Examiner has made no finding, with respect to novelty or inventive step, that a signaling aptamer complex, such as that claimed in the confliction application, lacks unity of invention with any of the instant methods of using that complex. On the contrary, the Examiner finds the instant processes of using a signaling aptamer complex are obvious methods of using the signaling aptamer complex claimed in conflicting application 10/502190.

With regard to instant claims 20 and 21, Applicant argues further kits comprising a substrate, a signaling aptamer that binds said substrate, and an enzyme capable of acting on said substrate are not obvious in view of the signaling aptamer complex claimed in the conflicting '190 application. The Examiner respectfully disagrees for the reasons given above in the ODP rejection. The Examiner further submits it was well established laboratory practice in both for-profit and not-for-profit enterprise to prepare laboratory reagents in advance of experimentation, storing said reagents in bottles, vessels, and other suitable containers, to make such reagents readily available to the researcher or laboratory as a whole or to the public in the interest of convenience, efficiency, and economy.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 8, 10, 13, and 14 remain rejected under 35 U.S.C. 102(e) as being anticipated by Gallivan (US Patent Application Publication 2003/0064931 A1).

The Examiner notes claim 7 was inadvertently included in the rejection statement in the previous Action. In fact, it is claim 8 that was examined in the previous Action, as explained at

page 2 of that Action. The Examiner apologizes for any confusion. The grounds of the rejection, however, as it pertains to independent claim 1, and claims depending thereon remains the same.

Gallivan disclosed aptamer constructs for monitoring and detecting a wide range of enzymatic activities. The aptamer is operably linked to a reporter gene encoding, for example, a fluorescent or toxic protein (paragraph 54). When bound to the preferred ligand, the aptamer may inhibit or enhance the expression of the reporter gene, resulting in a readily detectable signal (cell death or fluorescence) representative of changes in the concentration of the preferred ligand (paragraphs 61-70). Having high affinity for a first substrate and low or poor affinity for a reaction product of the substrate, the aptamer constructs are said to be useful for the detection of enzyme activities that convert one substance into another, wherein the aptamer preferably binds the precursor molecule but not the product. In the presence of the appropriate enzyme, a reduction in the levels of the precursor molecule results in a detectable signal, such as fluorescence, or, in the case of Examples 1 and 2, beginning at paragraph 78, cell survival. One of skill would recognize many variations of the aptamer constructs as disclosed therein for measuring and detecting enzyme-catalyzed reactions, wherein the signal produced would either decrease or increase depending on the design of the aptamer/expression construct, and whether the aptamer preferably binds the substrate or the product. In exemplary embodiments, Gallivan teaches using the method to detect the enzymes responsible for converting theobromine to caffeine and caffeing into theophylline (Examples 1 and 2, paragraphs 78-87).

Accordingly, Gallivan anticipates the claimed method.

Response to Arguments

Applicant argues the instant methods differ from those of Gallivan inasmuch as the instant methods are performed in a "test tube" and not inside a cell as in Gallivan. While the Examiner agrees the methods of Gallivan require intact living cells, the methods of Gallivan are designed to detect and measure freely diffusible substances in solution, wherein the substances diffuse into the cell where the aptamer is located. Ultimately, then, the methods of Gallivan results in a mixture or combination, wherein the substance and signaling aptamer commingle in solution, though inside a cell. Cells and cell-based assays may take place in any vessel, test tube or plate. The instant claims as now amended do not exclude cell-based assays. Therefore, Applicant argues a feature not recited in the instant claims. The steps of "mixing" and "adding" do not exclude mixing substances with or adding enzymes to cells. Neither the claims nor the specification offer any explicit, limiting definition of the term "mixture," such that "mixing" would exclude mixtures of cells and substances, and the claims do not currently require a cell-free mixture, nor do they require the signaling aptamer be outside a cell.

Applicant argues further the instantly claimed method "requires a signaling aptamer, which, according to the specification, is linked with a reporter molecule (for releasing a readily detectable signal)." This argument is not persuasive because although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). None of the instant claims requires an aptamer linked with a reporter molecule. The aptamer construct of Gallivan releases a signal inasmuch as it directly controls the translation and release into the cell of a reporter protein, which in turn may emit fluorescence, convert a substrate to a colored product, or produce cell death. Signal derives from the aptamer-target molecule interaction thereby.

Amending the claims to clearly exclude cell-based methods, or otherwise otherwise limit the claimed methods to cell-free mixtures would be remedial. As Applicant knows, all amendments must be explicitly, implicitly, or inherently supported by the application as filed.

***

Claims 1, 3, 5, 6, 13, and 14 remain rejected under 35 U.S.C. 102(b) as being anticipated by Tyagi et al. (1996) *Nat. Biotechnology* 14:303-308.

In describing the signaling aptamer of the instant invention, the specification teaches at page 9, paragraph 42, that "The signaling aptamer may be a molecular beacon as described in Tyagi and Kramer, 1996, incorporated herein by reference."

There is no disclosure or definition in the specification clearly precluding substance A and product B from being nucleic acids. The interpretation is consistent with the specification which teaches using signaling aptamers as real-time probes to report enzyme activities. Enzyme conversion of one substance into another reasonably includes the DNA polymerase-catalyzed chain reaction amplification of nucleic acids in which dNTP mononucleotides (substances A, B, C, and D) are converted into polymers of nucleic acid.

Tyagi et al. taught molecular beacons for monitoring the progress of polymerase chain reaction synthesis of a nucleic acid (page 304-5; Fig. 1). The beacon is designed to preferentially bind the amplification product (Product B). Accordingly, the beacon has highest affinity for the amplified sequence and lower or lowest affinity for the mononucleotide (ATP, GTP, CTP, and TTP) precursors (Substances A, B, C, and D), clearly meeting the requirements of claims 1, 3, and 10.

As described at pages 305-308 and shown in Fig. 7, in using molecular beacons to monitor the course of a polymerase chain reaction, Tyagi et al. taught steps for combining molecular beacons with substances A, B, C, and D, enzyme, primers, and buffer, determining the baseline fluorescence, and then monitoring for a change in fluorescence amplitude over time, as measured by the number of cycles. The increase in fluorescence is said to be indicative of binding of the beacon to the amplification product.

With regard to claim 5, the beacon (i.e., aptamer) comprises a quencher and fluorophore in proximity (Fig. 1).

With regard to claim 6, the hairpin-shaped beacon/aptamer comprises an aptamer oligonucleotide (the sequence that binds the amplification product) and quencher oligonucleotide (sequence comprising the quencher) capable of forming duplex with the aptamer oligonucleotide in the absence of an aptamer binding target (Fig. 1).

With regard to claims 13 and 14, by definition, a PCR reaction mixture represents a test sample, and the increase in fluorescene observed in the presence of the molecular beacon indicates the presence of a DNA polymerase, an enzyme. Pursuant to known enzyme kinetic principles, the rate of reaction and thereby the change in fluorescence would depend on the concentration of the enzyme as well as other components known to be essential to the PCR reaction.

Accordingly, Tyagi et al. taught every aspect of the instantly claimed method.

Response to Applicant's Arguments

Applicant cites external evidence (attached thereto as Exhibit 1) in arguing the limitation "aptamer" limits the claims to those nucleic acids that interact with binding partners by a lock-

and-key mechanism. At the outset, it is noted Exhibit 1 appears to be non-patent publication, but there is no disclosure of where or when it was published; whether it was part of an internal newsletter or a widely disseminated document available to the public at the time of invention. To be properly considered as objective evidence as it may bear on the patentability of the invention, the Exhibit should be submitted by way of an information disclosure statement, affidavit, or declaration. As submitted on 3/16/2009, the disclosure in Exhibit 1 may be considered as nothing more than part of the arguments of counsel, which cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Nevertheless, in the interest of expediting prosecution Exhibit 1 has been reviewed along with Applicant's remarks.

The arguments are not persuasive because the instant specification does not define aptamers to exclude those that bind nucleic acids. On the contrary, as explained in the rejection above, the instant specification clearly states at page 9 "The signaling aptamer may be a molecular beacon as described in Tyagi and Kramer, 1996…" Moreover, Exhibit 1 does not exclude molecular beacons. It states for example that an aptamer is a nucleic acid that binds tightly to a specific molecular target, and that aptamers may be obtained for a wide array of molecular targets. The fact that aptamers fold into three dimensional shapes does not exclude molecular beacons, since these too necessarily have secondary and tertiary structure. Accordingly, the Examiner fails to see how the definition offered by Exhibit 1 excludes the highly specific, thermodynamically favored, nucleic acid-nucleic acid interactions of the type formed between molecular beacons and their targets.

Applicant cites disclosure at paragraph 2 of the instant specification, stating that aptamers are nucleic acids with ligand-binding capabilities that are isolated from random sequence pools,

as a distinguishing feature. However, this definition is not found in the claims and is not set forth by the specification as a single, limiting definition. Morover, the beacon of Tyagi et al. has ligand-binding capability to the extend a "ligand" may be any molecule, including any nucleic acid, and the instant claims do not recite any product-by-process language that might in any way limit the invention to nucleic acids derived from random sequence pools. Finally, the claims remain extremely broad, embracing aptamers that bind any substance A, which as generically recited by the claims may be any small or large organic or inorganic molecule, including any protein or nucleic acid, lipid, or polysaccharide. Accordingly, the claims continue to read on the method of Tyagi et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 5, 6, 8, 11-14, 16-18, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tyagi et al. (1996) *Nat. Biotechnology* 14:303-308 in view of:

1. Li et al. (2002) *Biochem. Biophys. Res. Comm.* 292:31-40;
2. Gallivan (US Patent Application Publication 2003/0064931 A1);
3. Jhaveri et al. (2000) *J. Am. Chem. Soc.* 122:2469-2473; and
4. Hamaguchi et al. (2001) *Anal. Biochem.* 294:126-131.

The claims embrace the use of molecular beacon-like molecules comprising aptameric sequences for real-time detection of analytes produced during a chemical reaction. In some embodiments the reaction is enzyme-catalyzed. In more specific embodiments the enzyme is a phosphatase and the substrate is AMP.

Tyagi et al. is relied on for the reasons given above. Tyagi et al. taught molecular beacons for real time detection of nucleic acid amplification products, i.e., nucleic acid sequences, wherein upon binding the target nucleic acid sequence sample fluorescence increases due to separation of the quencher and flourophore regions of the molecular beacon. Tyagi et al. further taught monitoring the fluorescence thereafter to follow the progress of the reaction.

Gallivan is also relied on for the reasons given above. Gallivan showed that aptamers may be used to detect small molecule substances in a solution based on the conformational change in the aptamer upon binding said substance, which in turn results in production of a

reporter protein that may cause cell death, emit fluorescence, or produce a colored substrate (i.e., detectable signals).

Li et al. taught a variation of molecular aptamer beacons for the real time detection of proteins (pp. 31-40). Li et al. teach that their molecular aptamer beacon combines the signal transduction mechanism of molecular beacons and the molecular recognition specificity of aptamers (abstract, Fig. 1, and see introduction and results at pp. 31-39). Making direct reference to the molecular beacons developed by Tyagi et al., Li et al. taught that the basic concept of molecular beacons "can be adopted and broadened for the construction of MABs for proteins" (page 33), wherein fluorophore and quencher are attached to an aptamer at suitable positions such that upon binding of a target, such as a protein, the subsequence conformational change results in a change in the amplitude of the fluorescence signal released from the aptamer. The molecular beacon-aptamer concept is made quite clear by Li et al. In view of the routine nature of aptamer selection, it would have been obvious to one of skill in the art that the same method could be used for the detection of any molecule, small or large, based on the conformational-induced change in fluorescence of the molecular beacon-aptamer (see Li et al. in its entirety, e.g., Fig. 1).

Hamuguchi et al. echos and bolsters the teachings of Li et al., showing how to make and use molecular aptamer beacons for detecting proteins (pp.126-131). It is suggested the same constructs may be adapted for detection of other chemical compounds (abstract).

Jhaveri et al. taught a molecular beacon-like, adenosine/ATP binding fluorogenic aptamer for the detection of ATP and/or adenosine (Fig. 2b).

In each case cited above, the aptamer comprises quencher and fluorophore in proximity. In each case the references taught steps for incubating the aptamer with substrate and determining the amplitude of the fluorescent signal initially produced thereby. Furthermore, each reference builds directly upon the original concept developed by Tyagi et al., directly citing the original paper by Tyagi et al., and then showing how the MAB concept may be adapted for use with traditional aptamers for the detection of virtually any target molecule.

Accordingly, it was well known in the prior art that molecular beacons could be adapted for the detection of non-nucleic acid substances in real time in homogenous assays; that molecular beacons were compatible for use with enzyme-catalyzed reactions to detect products produced thereby; and that molecular beacon aptamers could be used to transduce molecular recognition into an optical signal. The prior art taught that to make a molecular aptamer beacon a suitable aptamer sequence may be incorporated into the loop region of the molecular beacon construct taught by Tyagi et al. to produce a ligand-sensitive beacon, which will undergo conformational change upon binding of the ligand to produce a fluorescent signal. For example, see Fig. 1, page 34, in Li et al., showing the typical structure of a molecular aptamer beacon.

Thus, methods for making and using molecular aptamer beacons for virtually any known substance were known in the art. More, generally, the prior art as a whole, represented by that cited herein, showed that the ligand-induced conformation change in an aptamer can be readily adapted for the detection of a wide variety of substances using the molecular beacon principle of flourophore-quencher or by regulation of reporter protein expression such as that disclosed by Gallivan.

Accordingly, given that the purpose of said beacons was to detect the presence or absence of a particular analyte in solution, it would have been obvious at the time of invention that such aptamer beacons could be used to monitor the increase in concentration of a given ligand in real time as occurs during the course of an enzyme-catalyzed reaction in the same manner taught and shown by Tyagi et al. to monitor the formation of a nucleic acid sequence during a polymerase-catalyzed polymerization of nucleoside triphosphosphates. Given that the prior art further showed that molecular beacons may be adapted or modified for detection of other substances such as proteins and small molecules, including adenosine or ATP, one of skill would have reasonably predicted that molecular aptamer beacons may be used in a wide variety of assays to detect the formation of any number of substances, as occurs during the course of an enzyme catalyzed reaction.

Given that the prior art cited herein recommended molecular aptamer beacons for their sensitivity and target specificity, one of skill would have been led to use molecular aptamer beacons in diagnostic assays. One such assay is that described by Jhaveri et al. for the detection of adenosine or ATP, known metabolic intermediates of significance to cellular processes. Other assays include the synthesis of proteins or nucleic acids, as taught by Li et al. and Tyagi et al.

Accordingly, in the absent of convincing evidence to the contrary, the instantly claimed invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Response to Arguments

Applicant argues none of the references, alone or in combination, suggest the methods of the instant claims. The Examiner respectfully disagrees for the reasons given in the rejection,

amplified above to address Applicant's arguments as to each reference individually. The instant claimed methods, as now claimed, represent an obvious variation of known methods for using the known characteristics of aptamers to undergo conformation change upon ligand binding together with the known molecular beacon technology, first developed by Tyagi et al. Moreover, as explained above, real-time detection of enzyme activity using aptamers was not novel, as shown by Tyagi et al. and Gallivan, who used nucleic acid aptamers, as defined by the instant application, to monitor DNA polymerase and metabolic enzymes in solution in real time. Clearly, as shown by the additional references cited herein, such methods would readily have been adapted by those of skill to detect proteins and small molecule substances. Given that the methodology is touted for diagnostic and research purposes, and molecular biological principles involving the potential correlation between an abnormal enzyme activity and disease, it would have been obvious to use these same aptamer-biosensing methods in any number of ways during the course of standard laboratory research to identify means of inhibiting such activity,

It is noted that Applicant's contribution to the art may have to do with the development of a bipartite aptamer complex, as recited in claim 6. (It is noted claim 6 does not capture each of the characteristics the tripartite complexe shown in Fig 1). However, this alone does not distinguish over the prior art because it, too, makes use of the same principle originally shown by Tyagi et al., wherein fluorophore and quencher are proximal in the aptamer, such that fluorescence is low prior to ligand binding, and high after binding. Whereas the beacon of Tyagi et al. and variants thereof disclosed by the prior art rely on intramolecular binding to keep quencher and fluorophore proximal, the complex of claim 6 would appear to rely on intermolecular interactions. Thus, claim 6 simply makes separate what was originally whole.

(Moreover, the complex of claim 6 does not use the word “separate" or “non-covalent” to clearly exclude single molecule aptamers such as those represented by the prior art cited herein. Thus, claim 6 continues to embrace single molecule aptamers.) Additionally, even if claim 6 were interpreted to embrace only bipartite aptamers composed of non-covalently bound oligonucleotides, one of skill would reasonably have envisioned these aptamers based on the known modular design of the aptamer molecular beacon (flurorophore and quencher domains) and predicted that, whether whole or separate, the beacon aptamer technique would function in substantially the same manner and produce substantially the same result. Nevertheless, with regard to claim 6, this rejection is rebuttable by objective evidence of surprising or unexpected results.

Applicant asserts the claims distinguish over the prior art inasmuch as they require signal release, quantifying enzyme concentration, screening for enzyme inhibitors, and detection of enzyme substrates. However, while no one reference discloses the complete method, the combination as a whole suggested each of these limitations for detecting enzyme activity and substrate catabolism and anabolism. Signal release, as generically recited, is shown. The versatility of aptamers as biosensors of enzyme and substrate is amply demonstrated by the prior art, and variations and adaptations of this methodology would have been immediately suggested thereby. One of skill in the art would have recognized, for example, the capability such methods for detecting essentially any substance, based on the aptamer art, represented herein, teaching that aptamers can be identified for essentially any known, isolatable substance.

It is further respectfully pointed out that the essential principle of the aptamer-based detection of substances shown by the prior art relies on the specific and selective affinity of an

aptamer for one substance over every other, including any structural derivative of that substance; therefore, every aptamer has a first and second affinity; these characteristics are inherent to aptamers.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Primary Examiner, Art Unit 1635
April 27, 2009